Typing Aberrance in Signal Transduction

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Abstract. We have developed a calculus, called *Ipi*, for describing the aberrance in biological models. Our approach extends the traditional pi calculus to handle aberrant process in the signal transduction. In this paper we propose a typing system that replaces the tag system of Ipi calculus. It is shown that the typing system is equal to the tag system in terms of the expressive power.

1 Introduction

There are several pieces of related work about modelling various biological systems based on pi calculus [1, 6], some of which are about modelling signal transduction (ST) [4, 5, 2, 3]. In these works however the biological systems are considered under normal conditions, assuming that there are no exceptions when they evolve.

In fact, part of the purpose of this research is to investigate the ways in which the biological systems can be subverted. There is an important reason for modelling these systems in all their complexity: many drugs and natural defenses work by subverting natural pathways. We need to model the aberrant biological systems to understand them. For this purpose, we have introduced Ipi calculus [8], extended from pi calculus, to describe more complex biochemical systems like aberrant ST. The calculus is obtained by adding two aberrant actions into pi calculus and a tag system to check existing aberrance.

We used the tag system to check the existence of aberrance in [8] by sets computation, such as union, disjoint, etc. It is quite intuitive but difficult to implement. Biological systems however are most complicated systems, so without an automatic tool we can hardly go any further. In this paper we introduce a

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typing system that is simple enough to be enforced statically and that is easily implemented into an automatic tool design (It had been implemented by Simon Gay). We will establish some properties of the typing system and show that it is equivalent to the tag system of [8].

2 The Pure Ipi Calculus

In this section we present the pure version of Ipi calculus that serves as the preliminary setting for our formal work. The pure Ipi calculus is Ipi calculus without the tag system.

2.1 Syntax

Processes evolve by performing actions. In process algebra actions capabilities are introduced by prefix capabilities. In Ipi calculus, we introduce two capabilities in addition to the prefix defined by pi calculus.

We assume that an infinite countable set $\mathcal{N}$ of names and an infinite countable set $\mathcal{V}$ of variables. Let $a, b, \cdots$ range over the names and $x, y, \cdots$ range over the variables. We also define two symbols § and ♯ to represent the aberrance capability. Here § represents the killer capability and ♯ the propagation capability. When a process has the killer capability, it terminates immediately. And when a process has the propagation capability, it will duplicate itself infinitely.

Definition 1 (Prefix). *The prefix of Ipi calculus are defined as follows:*

$$\pi ::= \overline{a}(b) \mid a(x) \mid \overline{a} \mid a \qquad \pi_i ::= \pi \mid \S(\pi_i) \mid \sharp(\pi_i)$$

The capability of π is the same as in pi calculus. $\S(\pi_i)$ and $\sharp(\pi_i)$ are the substitution capabilities. They are respectively the capabilities § and ♯ if the subject of π is in an aberrant state.

Definition 2 (Process). *The Ipi processes are defined as follows:*

$$P ::= 0 \mid \pi_i.P \mid \pi_i.P + \pi_i'.P' \mid P|P' \mid (\nu a)P \mid P; P'$$

Intuitively the constructs of Ipi processes have the following meaning: 0 is the inert process. The prefix process $\pi_i.P$ has a single capability imposed by π_i, that is, the process P cannot proceed until that capability has been exercised. The capabilities of the sum $\pi_i.P + \pi_i'.P'$ are those of $\pi_i.P$ plus those of $\pi_i'.P'$. When a sum exercises one of its capabilities, the other is rendered void. In the composition process $P|P'$, the components P and P' can proceed independently and can interact via shared channel. In the restriction process $(\nu a)P$, the scope of the name a is restricted to P. The sequential process $P; P'$ can run the process P' after the process P.

We write $fn(P)$ for the set of names free in process P, and $fv(P)$ for the set of variables free in P. An expression is closed if it has no free variables. Notice that a closed expression may have free names.

2.2 Semantics

The structural congruence $\equiv$ is the least equivalent relation on closed processes that satisfies the following equalities:

$$\begin{gathered} P \mid Q \equiv Q \mid P \\ (P \mid Q) \mid R \equiv P \mid (Q \mid R) \\ P + Q \equiv Q + P \\ (P + Q) + R \equiv P + (Q + R) \\ (\nu a)0 \equiv 0 \\ (\nu a)(\nu b)P \equiv (\nu b)(\nu a)P \\ ((\nu a)P) \mid Q \equiv (\nu a)(P \mid Q) \text{ if } a \notin fn(Q) \end{gathered}$$

The reaction relation, introduced initially by Milner [1], is a concise account of computation in the pi calculus. In addition to the well-known interaction rule(Com-N), our reaction relation also includes two new rules about reactions with aberrance(Pre-§ and Pre-♯).

$$\frac{}{\S(\pi_i).P \longrightarrow 0} \text{ Pre-§ ;} \qquad \frac{}{\sharp(\pi_i).P \longrightarrow \pi_i.P; \sharp(\pi_i).P} \text{ Pre-♯ ;}$$

$$\frac{}{\overline{a}(b).Q \mid a(x).P \longrightarrow Q|P\{b/x\}} \text{ Com-N;}$$

$$\frac{P \longrightarrow P'}{P + Q \longrightarrow P'} \text{ Sum;} \qquad \frac{P \longrightarrow P'}{P \mid Q \longrightarrow P' \mid Q} \text{ Com;}$$

$$\frac{P \longrightarrow P'}{(\nu a)P \longrightarrow (\nu a)P'} \text{ Res;} \qquad \frac{Q \equiv P \quad P \longrightarrow P' \quad P' \equiv Q'}{Q \longrightarrow Q'} \text{ Stc.}$$

The first two rules deal with reactions with aberrance: the former says that the resulting process is terminated; the latter declares that the resulting process duplicates itself infinitely. The third reaction rule deals with the interaction in which one sends a message with a channel while the other receives a message with the same channel so that they have an interactive action. Each of the reduction rules are closed in the summation, composition, restriction and structural congruence.

3 An Example in ST Pathway with the Aberrance

In order to illustrate the use of our calculus, we consider an example in ST pathway with aberrance. We focus our attention on the well-studied RTK-MAPK pathway. Here we choose a small yet important part, *Ras* Activation, for explanation.

Fig.1 gives an example of Ras Activation of the ST pathway, RTK-MAPK. At the normal state, the protein-to-protein interactions bring the SOS protein close to the membrane, where Ras can be activated. SOS activates Ras by exchanging Ras's GDP with GTP. Active Ras interacts with the first kinase in the MAPK cascade, Raf. GAP inactivates it by the reverse reaction.

Within the framework of Ipi calculus, we set some principles for the correspondence. Firstly, we choose the functional signaling *domain* as our primitive *process*. This captures the functional and structural independence of domains in signaling molecules. Secondly, we model the component *residues* of domains as communication *channels* that construct a process. Finally, molecular interaction and modification is modelled as communication and the subsequent change of channel names. Aviv Regev and his colleagues have given the representation of normal RTK-MAPK using the pi calculus [4].

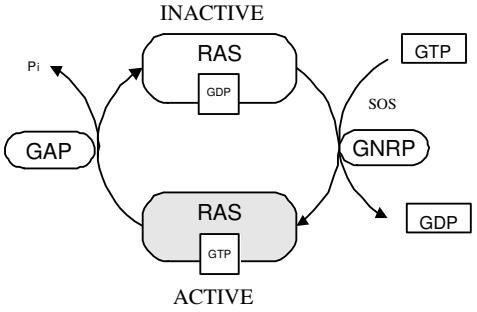

Fig.1. Ras Activation

A protein molecule is composed of several domains, each of which is modelled as a process as well. In (1) through (4) the detailed Ipi calculus programs for the proteins Ras, SOS, Raf and GAP are given:

$$RAS ::= INASWI\_I \mid INASWI\_II \tag{1}$$

$$SOS ::= S\_SH3\_BS \mid S\_GNEF \tag{2}$$

$$\begin{aligned} RAF ::= {} & R\_Nt \mid R\_ACT\_BS \mid R\_M\_BS \\ & \mid INA\_R\_Ct \mid R\_ATP\_BS \end{aligned} \tag{3}$$

$$GAP ::= sg(c\_ras).\overline{c\_ras}(gdp).GAP \tag{4}$$

The molecules (or domains) interact with each other based on their structural and chemical complementarity. Interaction is accomplished by the motifs and residues that constitute a domain. These are viewed as channels or communication ports of the molecule:

$$INASWI\_I ::= \overline{bbone}.ACTSWI\_I \tag{5}$$

$$INASWI\_II ::= \overline{sg}(rs\_1).rs\_1(x).bbone.ACTSWI\_II \tag{6}$$

$$S\_GNEF ::= bbone.S\_GNEF + sg(c\_ras).\overline{c\_ras}(gtp).S\_GNEF \tag{7}$$

The following interactions are possible:

$$INASWI\_I \mid S\_GNEF \longrightarrow ACTSWI\_I \mid S\_GNEF \tag{8}$$

$$INASWI\_II \mid S\_GNEF \longrightarrow bbone.ACTSWI\_II \mid S\_GNEF \tag{9}$$

The interaction (8) shows that the domain $INASWI\_I$ of Ras is activated by the domain of S_GNEF of SOS. The interaction (9) shows that the domain $INASWI\_II$ of Ras is activated by the domain S_GNEF of SOS.

The detailed Ipi programs for activated domains, $ACTSWI\_I$, $ACTSWI\_II$ of the protein Ras and the domain R_Nt of Raf are defined in (10) through (12):

$$ACTSWI\_I ::= \overline{s}(rs\_2).\overline{rs\_2}.ACTSWI\_I + \overline{bbone}.INASWI\_I \quad (10)$$

$$ACTSWI\_II ::= \overline{sg}(r\_swi\_1).r\_swi\_1(x).\overline{bbone}.ACTSWI\_II \quad (11)$$

$$R\_Nt ::= s(c\_ras).c\_ras.ACTR\_Nt \quad (12)$$

The processes so defined have the following interactions:

$$ACTSWI\_I \mid R\_Nt \longrightarrow^* ACTSWI\_I \mid ACTR\_Nt \quad (13)$$

$$ACTSWI\_II \mid GAP \longrightarrow^* \overline{bbone}.ASWI\_II \mid GAP \quad (14)$$

$$\overline{bbone}.ACTSWI\_II \mid ACTSWI\_I \longrightarrow INASWI\_II \mid INASWI\_I \quad (15)$$

The interaction (13) shows that the active domain $ACTSWI\_I$ of Ras interacts with the domain R_Nt of Raf. (14) shows that GAP inactivates the domain $ACTSWI\_II$ of Ras. (15) says that the domains of Ras interact with each other and that Ras rollbacks to the initial inactivated state.

When Ras mutates aberrantly, it does not have any effect on the Ras's binding with GTP but will reduce the activity of the GAP hydrolase of Ras and lower its hydrolysis of GAP greatly; in the meantime Ras will be kept in an active state; they keep activating the molecule, inducing the continual effect of signal transduction, which result in cell proliferation and tumor malignancy.

(16) defines the Ipi representation of GAP in the aberrant state. (17) shows that GAP loses its function and does nothing, meaning that it can not inactivate the domain $ACTSWI\_II$ of Ras.

$$GAP ::= \S(sg(c\_ras)).\overline{c\_ras}(gdp).GAP \quad (16)$$

$$GAP \longrightarrow 0 \quad (17)$$

But then the interaction (15) will not occur whereas the interaction (13) will occur infinitely. Now observe that

$$\sharp ACTSWI\_I \longrightarrow ACTSWI\_I; \sharp ACTSWI\_I$$

It reaches an abnormal state with exceptions. Pi calculus could not easily describe this aberrant case. Ipi calculus, on the contrary, can describe it quite precisely.

4 The Tag System

The occurrence of aberrance is affected by temperature, environment, and concentration, etc. We will express the aberrance using two functions. We assume

an infinite countable set $\mathcal{A}$ of values. Let σ, ρ be functions from $\mathcal{N}$ to $\mathcal{A}$. One can think of σ as an interference function and that $\sigma(a)$ as the interference degree of a. The function ρ is a critical function and that $\rho(a)$ is the critical value of the interference degree of a. The interference coefficient can be defined below:

Definition 3 (Interference Coefficient). *For $a \in \mathcal{N}$, let i_a be $|\rho(a) - \sigma(a)|$. We say that i_a is the interference coefficient of a.*

Therefore, when the aberrance occurs, it will be marked into the interference coefficient. We call such a system the tag system of Ipi calculus. Intuitively, when i_a is equal to zero, we take that a is in an aberrant state; when i_a is not zero, we think that a is still in a normal state. For convenience of representation, when i_a is equal to zero, we write 0 as the tag of a. Otherwise we write i_a as the tag of a.

For every prefix, we write a pair $\langle i_{\pi_i}, \pi_i \rangle$ instead of π_i, where i_{π_i} is the tag of π_i. When $\pi_i = \pi$, i_{π_i} is the tag of the subject of π; when $\pi_i = \S(\pi_i')$ or $\pi_i = \sharp(\pi_i')$, $i_{\pi_i} = 0$.

For a process, the expression of a process is also a pair $\langle I_P, P \rangle$ where I_P is the tag of the process P. The syntax of the tags is defined inductively by the following rules, where the symbol $\uplus$ means disjoint union: $\overset{\infty}{\underset{n=1}{\uplus}} I_P \triangleq I_P \uplus I_P \uplus \cdots$:

$$\frac{}{I_0 = \emptyset} \text{ 0-t} \qquad \frac{\langle I_P, P \rangle = \langle i_\pi, \pi \rangle.\langle I_Q, Q \rangle}{I_P = \{i_\pi\} \uplus I_Q} \text{ N-t}$$

$$\frac{\langle I_P, P \rangle = \langle 0, \S(\pi_i) \rangle.\langle I_Q, Q \rangle}{I_P = \{0\}} \S\text{-t} \qquad \frac{\langle I_P, P \rangle = \langle 0, \sharp(\pi_i) \rangle.\langle I_Q, Q \rangle}{I_P = \overset{\infty}{\underset{n=1}{\uplus}} (\{0\} \uplus \{i_{\pi_i}\} \uplus I_Q)} \sharp\text{-t}$$

$$\frac{\langle I_P, P \rangle = \langle i_{\pi_i}, \pi_i \rangle.\langle I_Q, Q \rangle + \langle i_{\pi_i'}, \pi_i' \rangle.\langle I_R, R \rangle}{I_P = f(\langle \{i_{\pi_i}\} \uplus I_Q, \{i_{\pi_i'}\} \uplus I_R \rangle)} \text{ Sum-t}$$

$$\frac{\langle I_P, P \rangle = \langle I_Q, Q \rangle | \langle I_R, R \rangle}{I_P = I_Q \cup I_R} \text{ Com-t} \qquad \frac{\langle I_P, P \rangle = (\nu x)\langle I_Q, Q \rangle}{I_P = I_Q} \text{ Res-t}$$

$$\frac{\langle I_P, P \rangle = \langle I_Q, Q \rangle; \langle I_R, R \rangle}{I_P = I_Q \uplus I_R} \text{ Seq-t}$$

In the above definition, $\langle I_P, I_Q \rangle$ is a pair, f is the projection, and $f(\langle I_P, I_Q \rangle)$ represents the tag of the process which has the operator "sum". I_P and I_Q are nondeterministically chosen as the process P or Q is chosen to act.

Let I_P, I_Q be the tags of the processes P and Q. We define

$$I_P = I_Q \Leftrightarrow \langle I_P, P \rangle \equiv \langle I_Q, Q \rangle$$

So we have defined an equivalence on the tags in terms of the structural equivalence.

For the reaction relations, all the rules react with their tags reacting simultaneously. We define them as follows:

$$\frac{}{\{0\} \setminus \{0\} = \emptyset} \text{pre-}\S;$$

$$\frac{}{\biguplus_{n=1}^{\infty}(\{0\} \uplus \{i_{\pi_i}\} \uplus I_P) \setminus \{0\} = \{i_{\pi_i}\} \uplus I_P \uplus \biguplus_{n=1}^{\infty}(\{0\} \uplus \{i_{\pi_i}\} \uplus I_P)}\text{pre-}\sharp;$$

$$\frac{}{(\{i_x\} \uplus I_Q) \cup (\{i_x\} \uplus I_P) \setminus \{i_x\} = I_Q \cup I_P}\text{com-N};$$

$$\frac{I_P \setminus \{i_y\} = I_{P'}}{f_P(\langle I_P, I_Q\rangle) \setminus \{i_y\} = I_{P'}}; \qquad \frac{I_P \setminus \{i_y\} = I_{P'}}{I_P \cup I_Q \setminus \{i_y\} = I_{P'} \cup I_Q};$$

$$\frac{I_Q = I_P \quad I_P \setminus \{i_x\} = I_{P'} \quad I_{P'} = I_{Q'}}{I_Q \setminus \{i_x\} = I_{Q'}}.$$

The section is a brief introduction to the tag system. To know more, see [8].

5 The Typing System

As we have mentioned, for a biochemical network with aberrance, we hope to know whether the proteins are aberrant or not in the network. So in Ipi calculus, we need to control the information flow when modelling an aberrant biochemical network. This section describes rules for controlling information flow in Ipi calculus. There are several ways of formalizing those ideas, just like the tag system introduced in [8]. Here we embody them in a typing system for Ipi calculus. Typing system was firstly introduced by Martin Abadi in studying security protocols [7].

5.1 The Typing System

In order to represent the aberrance of ST we classify signals into three classes:

- A *Normal* signal is one that takes part in the normal processes.
- An *Aberrant* signal is one that takes part in the aberrant processes.
- An *Unknown* signal could be any signal.

To simplify we define a reflexive order relation $<:$ among these three classes:

Normal$<:$ *Unknown*;
Aberrant $<:$ *Unknown*.

For convenience of representation, we denote M as a name or a variable. M is called *term*. Corresponding to these three classes the typed system has three kinds of assertions:

- "$\vdash \Gamma$ well formed" means that the environment Γ is well-formed.
- "$\Gamma \vdash M : T$" means that the term M is of the class T in Γ.
- "$E \vdash P : ok$" means that the process P type checks in E.

Typing rules are given under an environment. An environment is a list of distinct names with associated classifications.

Definition 4 (Typed Environment). *Typed environments are given by the following rules:*

$$\frac{}{\vdash \emptyset \ well\ formed}\ Environment\ Empty$$

$$\frac{\vdash \Gamma \ well\ formed, M \notin \Gamma}{\vdash \Gamma, M : T \ well\ formed}\ Environment\ Term$$

Having defined the environments, one can define rules for terms and processes.

Definition 5 (Terms). *The rules for terms of typing system are as follows:*

$$\frac{\Gamma \vdash M : T \quad T <: R}{\Gamma \vdash M : R}\ Level\ Subsumption$$

$$\frac{\vdash \Gamma \ well\ formed \quad M : T \ in\ \Gamma}{\Gamma \vdash M : T}\ Level\ Term$$

Intuitively the rule Level Subsumption says that a term of level *Normal* or *Aberrant* has level *Unknown* as well.

Definition 6 (Processes). *The rules for typing processes are as follows:*

$$\frac{\Gamma \vdash a : Normal \quad \Gamma \vdash b : Normal \quad \Gamma \vdash P : Ok}{\Gamma \vdash \overline{a}(b).P : Ok}\ T\text{-}out$$

$$\frac{\Gamma \vdash a : Normal \quad \Gamma \vdash x : Normal \quad \Gamma \vdash P : Ok}{\Gamma \vdash a(x).P : Ok}\ T\text{-}in$$

$$\frac{\Gamma \vdash a : Normal \quad \Gamma \vdash P : Ok}{\Gamma \vdash \overline{a}.P : Ok}\ T\text{-}sout \qquad \frac{\Gamma \vdash a : Normal \quad \Gamma \vdash P : Ok}{\Gamma \vdash a.P : Ok}\ T\text{-}sin$$

$$\frac{\Gamma \vdash a : Aberrant \quad \Gamma \vdash b : Unknown \quad \Gamma \vdash P : Ok}{\Gamma \vdash \S(\overline{a}(b)).P : Ok}\ T\text{-}kout$$

$$\frac{\Gamma \vdash a : Aberrant \quad \Gamma \vdash x : Unknown \quad \Gamma \vdash P : Ok}{\Gamma \vdash \S(a(x)).P : Ok}\ T\text{-}kin$$

$$\frac{\Gamma \vdash a : Aberrant \quad \Gamma \vdash P : Ok}{\Gamma \vdash \S(\overline{a}).P : Ok}\ T\text{-}ksout \qquad \frac{\Gamma \vdash a : Aberrant \quad \Gamma \vdash P : Ok}{\Gamma \vdash \S(a).P : Ok}\ T\text{-}ksin$$

$$\frac{\Gamma \vdash a : Aberrant \quad \Gamma \vdash b : Unknown \quad \Gamma \vdash P : Ok}{\Gamma \vdash \sharp(\overline{a}(b)).P : Ok}\ T\text{-}pout$$

$$\frac{\Gamma \vdash a : Aberrant \quad \Gamma \vdash x : Unknown \quad \Gamma \vdash P : Ok}{\Gamma \vdash \sharp(a(x)).P : Ok}\ T\text{-}pin$$

$$\frac{\Gamma \vdash a : Aberrant \quad \Gamma \vdash P : Ok}{\Gamma \vdash \sharp(\overline{a}).P : Ok}\ T\text{-}psout \qquad \frac{\Gamma \vdash a : Aberrant \quad \Gamma \vdash P : Ok}{\Gamma \vdash \sharp(a).P : Ok}\ T\text{-}psin$$

$$\frac{\vdash \Gamma \ well\ formed}{\Gamma \vdash 0 : Ok}\,T\text{-}nil \qquad \frac{\Gamma, a : Normal \vdash P : Ok}{\Gamma \vdash (\nu a)P : Ok}\,T\text{-}res$$

$$\frac{\Gamma \vdash P : Ok \quad \Gamma \vdash Q : Ok}{\Gamma \vdash P \mid Q : Ok}\,T\text{-}com \qquad \frac{\Gamma \vdash P : Ok \quad \Gamma \vdash Q : Ok}{\Gamma \vdash P + Q : Ok}\,T\text{-}sum$$

$$\frac{\Gamma \vdash P : Ok \quad \Gamma \vdash Q : Ok}{\Gamma \vdash P; Q : Ok}\,T\text{-}seq$$

5.2 Properties of Typing

Having defined the typing system for Ipi calculus, we can show that the checking capability of the typing system is equal to the tag system of [8]. We firstly establish some properties of typing system before proving the main result. The first three are fundamental properties satisfying a typing system. The last one is a precondition for the theorem. The proofs of properties are obvious so we omit them here.

Proposition 1. *Assume that $\vdash \Gamma$ well formed and that the terms in $dom(\Gamma)$ are all normal. Then the following properties hold:*

- *If M is a term and $M \in dom(\Gamma)$, then $\Gamma \vdash M : Normal$.*
- *if P is a process with $f_n(P) \cup f_v(P) \subseteq dom(\Gamma)$, then $\Gamma \vdash P : ok$.*

Proposition 2 (Strengthening). *Assume that the term M is not free in the process P and that $N \neq M$. The following properties hold:*

- *If $\Gamma, M : T \vdash N : S$, then also $\Gamma \vdash N : S$.*
- *If $\Gamma, M : T \vdash P : Ok$, then also $\Gamma \vdash P : Ok$.*

Proposition 2 enables us to condense an environment, moving out the declaration of a term that is not used.

Proposition 3 (Weakening). *Let M is not defined on the environment Γ,*

- *If $\Gamma \vdash N : S$, then $\Gamma, M : T \vdash N : S$.*
- *If $\Gamma \vdash P : Ok$, then $\Gamma, M : T \vdash P : Ok$.*

Proposition 3 declares that anything that can be proved in a given environment can also be proved with more assumptions.

Proposition 4 (Signal checking). *Let i_M be the interference coefficient of the term M. Then*

- *$i_M = 0$ if and only if $M : Aberrent$;*
- *$i_M \neq 0$ if and only if $M : Normal$.*

Now, we bring out the key theorem of this paper, presented as follows. It can be concluded that the typing system is equal to the tag system in terms of the expressive power.

Theorem 1 (Full Abstraction). *Let I_P be the tag of P. Then $0 \in I_P$ iff 'If $\Gamma \vdash P : ok$, then there is a term M in P such that $\Gamma \vdash M : Aberrant$'.*

It can be proved by induction on the derivation of I_P and the P.

With this brief typing system, we can verify the aberrant ST pathways without complex tags, and implement into an automatic tool to run it correctly.

6 Future Prospects

This work brings out the static checking for Ipi calculus, opening up new possibilities in the study of biochemical systems with exceptions. Our next work is to investigate properties of Ipi calculus, finding out the relations between these properties and the properties of biochemical systems.

We can also modify the typing system to suit for regulating various biochemical systems, including transcriptional circuits, metabolic pathways etc. Also, while we get further knowledge of biochemistry, we will refine our typing system in a more precise way to type check errors when we design automatic tools.

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